REMARKS

The issues outstanding in the Office Action mailed January 22, 2008, are the objection to the claims, the Information Disclosure Statement, and the rejections under 35 U.S.C. 112, 101, 102, 103 and the doctrine of obviousness-type double patenting. Reconsideration of each of these issues, in view of the following discussion, is respectfully requested. The following discussion follows the order of the paragraphs of the Office Action.

Objections

Claim 1 has been objected to because of a typographical error. Appropriate correction has been made, and withdrawal of this objection is respectfully requested.

Claim 6 has been objected to under 37 C.F.R. 1.75 (c), as being of improper dependent form by failing to further limit the subject matter of claim 1, upon which it depends. The typographical error in claim 1, in which the definition of X was omitted, has been remedied. Supplying of the definition of X is supported in the present specification, for example, by the proviso at the end of claim 1 (indicating that X can be CH) and from the specification at page 10, last line, where it is indicated that X is preferably N. Withdrawal of this objection is therefore also respectfully requested.

Information Disclosure Statement

It is apparent that the International Bureau has not furnished the references cited in the International Search Report, contrary to the required procedure. Copies of the two references lined through on the previous form 1449, along with an additional form 1449 listing these references, is provided herewith. It is respectfully requested that the Examiner return an initialed form 1449.

Rejections Under 35 U.S.C. 112

Claims 1-20 [sic, "1-17"] are rejected under 35 U.S.C. 112, first paragraph. Reconsideration of this rejection is respectfully requested.

At page 3 of the Office Action, it is admitted that the specification enables enantiomers, mixtures of enantiomers, and racemates of compounds of formula I. However, it is argued that the specification does not provide enablement for "solvates" of compounds of formula I. Applicants respectfully disagree with this analysis. It appears that the Office Action alleges that the formation of solvates is not enabled because, e.g., the formation of solvates is unpredictable. In support, the Office Action quotes a passage from *Vippagunta* which indicates that certain predictions about solvates or hydrates of a compound are complex and difficult.

However, the Office Action appears to ignore within the same document the passages which show the claims are enabled. For example, *Vippagunta* on page 15, top of first column, states that

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement that

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling ... Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states that

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. ...
> The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* throughout the reference teaches various solvates, hydrates, etc., structural aspects thereof, examples thereof, including preparation techniques, and methods/techniques for the characterization thereof. See, e.g., pages 15-18.

While it may be true, that the prediction of what a particular solvate of a compound will actually look like, e.g., whether one, 3 ½, 6 or 12 solvent molecules are incorporated, the Office Action is incorrect with respect to the alleged lack of enablement.

Even the very paper cited in support of the rejection demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates

and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See extensive list of techniques identified on column 2 of page 18.

Additionally, based on the above discussed statistics in this field provided by *Vippagunta*, one of ordinary skill in the art would also have a good expectation for success. While certain predictions may be difficult in the art of forming solvates, the formation of solvates is common with pharmaceutically active ingredients and methods of detecting and characterizing them are well-known and widely applied routinely.

In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that there is no lack of enablement.

Thus, the Office Action has not carried its burden in establishing a lack of enablement because the Office Action has not established any basis to doubt objective enablement. See *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971) holding that a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) See also *In re Bundy*, 209 USPQ 48 (1981) holding that the "PTO must have adequate support for its challenge to the credibility of applicant's statements of utility," which statements were made in *Bundy* in the context of an enablement rejection, and which is lacking in the present case. In view of the state of the art, it is evident that there is no indication that one of ordinary skill in the art would have questioned that solvates could be formed. See *Rasmusson v. Smithkline Beecham Co.*, 75 USPQ2d 1297 (Fed.Cir. 2005).

Nevertheless, applicants provide further information clearly demonstrating that solvate formation is a common phenomenon among pharmaceutical substances, i.e., Polymorphism: in the pharmaceutical industry (edited by *Ralf Hilfiker*; 2006 Wiley-VCH), Chapter 8, The Importance of Solvates, by *U. J. Griesser*, pp. 211-222 (hereinafter *Griesser*).

On page 220, *Griesser* teaches that

> Over almost two decades we carefully collected data on the solid-state properties of a few thousand pharmaceutically relevant

> organic compounds, with special focus on those drug substances listed in the Pharmacopoeia European (PhEur). The 1997 edition of PhEur contained 559 well-defined organic drug compounds. ... For more than 55% of them either polymorphs or solvates are known. In a newer evaluation of a larger set of data (PhEur edition 4.02, 8008 solid organic compounds ... this fraction increased only slightly to 57%. As shown in Fig. 8.4, 29% of the compounds are known to form hydrates, 10% other solvates ... (Emphasis added.)

Additionally, various factors in considering whether solvates would be expected to form are identified by *Griesser* on pages 220-221, e.g., salt forms, molecular size, lipophilicity. A citation is provided for ascertaining "further trends and interrelations between molecular properties and solvate/hydrate formation." See the middle of page 221. All this demonstrates that one of ordinary skill in the art would know or have guidance as to what factors to consider in expectation of success.

Moreover, under the section titled "Generation and Characterization of Solvates" on page 222, *Griesser* teaches that

> Since it is imperative to establish the crystal forms of an active pharmaceutical ingredient (API) to satisfy the regulatory authorities ..., solvates of drug compounds are now preferentially discovered in systematic polymorph screenings. ... **Automated crystallization systems and strategies** have been developed to speed up this process, **allowing thousands of crystallization experiments in a short time**. (Emphasis added.)

In view of the state of the art of solvate formation, e.g., solvate formation being a very common phenomenon associated with drug substances, the generation and examination of which is done with highly automated machines, the Office Action has not established that it would require undue experimentation by one of ordinary skill in the art to prepare and even characterize the solvates of a compound.

While the amount of work to prepare solvates of the compounds of the invention may require some effort or maybe even considerable effort (although not admitted), no undue experimentation is required in the preparation of solvates. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent

coupled with information known in the art without undue experimentation." *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988). One of ordinary skill in the art merely through routine laboratory efforts can take various compounds of the invention, which are explicitly admitted by the Office Action to be enabled at the top of page 3, bring them together with various solvents and check whether solvates have formed. This type of work is merely routine laboratory work and does not require undue experimentation. Moreover, as discussed in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the "test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine," which it is in the present case.

Moreover, although it is recognized that the Hilfiker text has published in 2006, the relevant passages that deal with the statistical aspects and frequency of solvates are (8.3, pp 219 ff.) based on data given in the Pharmacopoeia European (PhEur) which was published well before the priority date of the instant application, i.e. published in the 1997 (3rd edition), 2002 (4th edition) and February 2003 (supplement 4.02). According to this statistical data, solvates are common in the chemistry of pharmaceuticals and thus enabled. Additionally, the majority of the papers that are cited in the text are published before or around the priority date or the international filing date of the instant application. Thus, the Hilfiker text (i.e., the Griesser review article) gives a clear picture of what was known in the field of solvates around the priority/filing date of the instant application, and clearly supports enablement.

Moreover, attached to the present reply is secondary literature, i.e. articles cited as number 57, 63 and 64 in Griesser, and an additional article of U. J Griesser (Auer et al.), a co-author heavily cited by Griesser. The latter was received on July 20, 2003 and accepted in September 2003 and thus published in between the priority date and the international filing date of the instant application.

All those articles show that the skilled artisan was aware of solvates in the field of pharmaceutically active ingredients and that a plenty of methods for detecting them and producing them on a routine basis where already established before the priority/filing date of the instant application. Such methods include detection by infrared FT-Raman spectroscopy (e.g. in Auer et al.) and production by crystallization, spray drying and/or lyophilization (freeze-drying),

see e.g. Otsaka et al and Yu et al.. Byrn et al even show flowcharts for the systematic approach to the detection of solvates as early as 1995. Additionally, the article by Byrn et al shows that information on the polymorphic forms (of which solvates are the most frequent ones) was routinely asked for by regulatory offices around the world, including the FDA. Moreover, e.g. on page 951, section D, Byrn et al state that regularly an anhydrous drug product obtained can be partially or completely converted into hydrates (the most common form of solvates) by a method as simple as wet grinding.

It is therefore respectfully submitted that ample basis exists to withdraw the rejection under 35 U.S.C. 112, and the same is respectfully requested.

Claims 1-20 (again, presumably 1-17) are rejected under 35 U.S.C. 112, second paragraph. Various typographical errors in the claims have been corrected, which it is submitted addresses the issues raised at the top of page 5 of the Office Action. Withdrawal of this rejection is therefore respectfully requested.

Moreover, the claims reciting a "use" have been modified from their European format to be method claims, as common in U.S. practice. It is submitted that these claims are thus clear.

Rejection Under 35 U.S.C. 101

Claims 11-13 and 16 have been rejected under 35 U.S.C. §101, as a result of their non-standard U.S. format. Recasting of these "use" claims as method claims obviates this rejection, and withdrawal thereof is respectfully requested.

Rejections Under 35 U.S.C. 102

Claims 1-3, 5, 7, 10, 14 and 15 have been rejected under 35 U.S.C. §102(a) over Schiemann (WO '345). This commonly owned application was published on April 17, 2003. In view of the provision of the verified translation of the present priority document, having a date of April 5, 2003, it is submitted that this rejection is moot.

Claims 1-4, 10, 14 and 15 have been rejected under 35 U.S.C. 102(b) over Zhu (U.S. application 2002/0091116, published July 11, 2002). Reconsideration of this rejection is respectfully requested.

It is respectfully submitted that the example cited in the specification in no way anticipates the present claims. Examples 129, 130 and 140 disclose compounds which are 1-Aryl-2-yl-1H-pyrazole or 2H-Pyrazole-3-carboxylic acid amides, wherein Aryl is a bicyclic moiety. These compounds do not anticipate the presently claimed formula I, inasmuch as R_3 herein (much less R_2 or R_1) is not a carboxylic acid amide.

It is not known whether the definition to the variables postulated at page 6 of the Office Action are intended to represent the reference, or the present claims. In either case, there is an apparent error, inasmuch as no R6 appears in either the reference or the present claims, and, moreover, R_3 *cannot* have the definitions alleged in the Office Action, if the variable is intended to represent that in the present claims. It is not seen that a variable R_3 exists in the reference, as well.

As a result, the disclosure of this reference is easily dispensed with and withdrawal of this rejection is appropriate. The same is respectfully requested.

Claims 1-4, 7, 10, 14 and 15 have been rejected under 35 U.S.C. 102(b) over Xiang (WO 98/031227). Reconsideration of this rejection is also respectfully requedted.

It appears that the variables given at the top of page 7 are intended to represent the present claims. However, R_3 in the present claims cannot be $-O(CH_2)_2$–morpholine. R_3 is $(CH_2)_n$ het, contrary to the definition given at page 7 of the Office Action. Thus, Xiang does not anticipate the present claims, and withdrawal of the rejection is also appropriate, and respectfully requested.

Rejection Under 35 U.S.C. 103

Claims 1-4, 10, 14, 15 and 17 have been rejected under 35 U.S.C. 103 over Zhu (same reference as in the 102 rejection). Reconsideration of this rejection is also respectfully requested.

First, as noted above, the prior cited compounds of the reference are pyrazole-3-carboxylic acid amides, which are not within the scope of the present claims. Moreover, example 146, cited in this portion of the rejection, is directed to compounds in which a phenyl group, bonded to one of the nitrogen atoms of the five member ring, is further substituted by –

C(NH)-methyl-piperazine. Instead, R_6 in the present invention is $(CH_2)_nHet$ or $(CH_2)_nAr$. It is not seen how this divergent structure in the reference could suggest the presently claimed compounds, for at least these 2 significant structural differences. There is no way that this compound could be construed a "homolog", as alleged at page 8 of the Office Action. Withdrawal of this rejection is therefore also appropriate, and is respectfully requested.

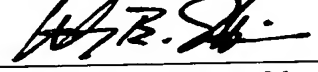
Double Patenting

Claims 1-7, 10, 14, 15 and 17 have been rejected under the doctrine of obviousness-type double patenting over claims 1, 2 and 4-17 of co-pending application serial no. 10/552,064. In addition, claim 1 has been rejected under the doctrine of obviousness-type double patenting over claim 1 of co-pending application 10/552,065. It is submitted that the attached Terminal Disclaimer obviates these rejections.

It is submitted that all claims are in condition for allowance, and passage to issue is respectfully requested. However, should the Examiner have any questions or comments, he or she is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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